Pegylated Interferon (Peg-Ifn) Monotherapy for HBeAg-Positive and Negative Chronic Hepatitis B (CHB)

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Standard Interferon (sIFN) Alfa, the first therapy proven effective for CHB, has been largely used for the treatment of compensated liver disease due to HBV in the last two decades. Two forms of PEG-IFNs (alfa2a and alfa2b), with improved pharmacokinetics, have been more recently evaluated in randomised clinical trials of different design.

PEG-IFN vs. sIFN
Three doses of PEG-IFN-alfa2a (90 ug, 180 ug, 270 ug given qw) were compared to 4.5 MU tiw of sIFN-alfa2a for 24 weeks in 194 HBeAg positive patients. PEG-IFN-alfa2b (1 ug/Kg qw) was compared to sIFN-alfa2b (3 MU tiw) for 24 weeks in another study with 230 HBeAg positive Chinese patients. In both studies, rates of HBeAg loss 6 months after therapy were significantly higher with PEG-IFN, but the effect on other virological and biochemical endpoints was similar with the two treatments. Overall, the evidence for superiority of PEG-IFNs appeared weak, considering also that both types of sIFN were used at low doses.

PEG-IFN monotherapy in HBeAg-positive CH
PEG-IFN-alfa2a (180 ug/week) monotherapy was compared to Lamivudine (100 mg/daily) monotherapy and PEG-IFN plus Lamivudine combination therapy in 814 patients treated for 48 weeks. Taking as endpoint the response at 6 months after therapy, PEG-IFN monotherapy was significantly better than Lamivudine monotherapy as to HBeAg seroconversion (32% vs 19%), HBV-DNA suppression <100,000 copies/mL (32% vs 22%), and combined response (23% vs 10%). Durability of response, assessed 1 year after therapy only in a subgroup of patients (486 out of 814) enrolled in a long-term observational study, was between 80 and 86%. By multivariate analysis, response to PEG-IFN was associated with pre-treatment higher ALT and lower HBV-DNA and HBeAg levels, but not with gender, age, race, body weight. Genotype A (HBV-A) showed somehow better response (52%) compared to HBV-B (30%), HBV-C (31%), and HBV-D (22%).

In another randomised trial, PEG-IFN-alfa2b monotherapy (100 ug/week during weeks 1-31 and 50 ug/week during weeks 32-52) was assessed in 136 HBeAg-positive patients in comparison with PEG-IFN plus Lamivudine combination therapy. Twenty-four-week sustained response rates with PEG-IFN monotherapy were: HBeAg loss 36%, HBeAg seroconversion 29%, HBV-DNA < 200,000 copies/mL 27%, HBV-DNA < 400 copies/mL 7%, HBsAg loss 7%, ALT normal 32%. By multivariate analysis response (HBeAg loss) was associated with pre-treatment higher ALT and lower HBV-DNA and with ALT flares accompanied by HBV-DNA reduction during therapy. Patients with HBV-A and HBV-B had better response (HBeAg and HBsAg loss) compared to those with HBV-C and HBV-D.

PEG-IFN monotherapy in HBeAg-negative CHB
PEG-IFN-alfa2a (180 ug/week) monotherapy has been investigated in 177 HBeAg-negative patients and compared to Lamivudine monotherapy and to PEG-IFN plus LAM combination therapy for 48 weeks. Taking as endpoint the response at 6 months after therapy, PEG-IFN was significantly better than LAM for HBV-DNA suppression <20,000 copies/mL (43% vs. 29%), ALT normalisation (59% vs. 44%), and combined response (36% vs. 23%). More

profound HBV-DNA suppression (<400 copies/mL) was seen in 19% vs. 7%. Durability of the response at longer follow-up, assessed only in a subgroup of 116 patients enrolled in an observational study, was seen in 73% of the patients followed for 1 year after therapy. No strong predictors of response to PEG-IFN monotherapy could be identified. There was a trend for better response with higher baseline ALT and lower EOT-HBV-DNA. Race, gender, age had no effect. Stratification by HBV genotypes was difficult due to the limited numbers of cases in each group.

PEG-IFN in Lamivudine-resistant patients

In the only study in which YMDD mutants were investigated at baseline, levels of LAM-resistant virus correlated with reduced HbeAg response to PEG-IFN-alfa2b monotherapy.

Safety

PEG-IFN monotherapy was in general well tolerated, being similar to sIFN (by direct and historical comparison). Neutropenia was the most common reason for dose reduction or early discontinuation, events that were both more common in patients with cirrhosis.

Conclusions

PEG-IFN monotherapy is associated with a 24-week sustained anti-HBe seroconversion in around 30% of HBeAg-positive and a 48-week sustained HBV-DNA<100,000 copies suppression in around 30% of HBeAg-negative patients with compensated CHB. Many issues are still unsolved:

1) Definition of more standardised endpoints
2) Long-term durability of response, particularly in HbeAg-negative cases
3) Optimised dose and duration of treatment
4) Predictors of response and early identification of non-response and stopping rules
5) Long-term effects on infection and disease outcomes, also in comparison with oral antivirals and optimised suppressive therapies
6) Superiority vs. standard IFNs

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